WILMER, CUTLER & PICKERING
2445 M STREET, N.W.
WASHINGTON, D.C. 20037-1420

TELEPHONE (202) 663-6000
FACSIMILE (202) 663-6363

NEIL J. KING
DIRECT LINE (202) 663-6061

100 LIGHT STREET
BALTIMORE, MD 21202
TELEPHONE (410) 986-2800
FACSIMILE (410) 986-2828

4 CARLTON GARDENS
LONDON SW1Y 5AA
TELEPHONE 011 (44171) 872-1000
FACSIMILE 011 (44171) 839-3537

RUE DE LA LOI 15 WETSTRAAT
B-1040 BRUSSELS
TELEPHONE 011 (322) 285-4900
FACSIMILE 011 (322) 285-4949

FRIEDRICHSTRASSE 95
D-10117 BERLIN
TELEPHONE 011 (4930) 2022-6400
FACSIMILE 011 (4930) 2022-6500

March 13, 1998

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Ninth Report on Carcinogens

Dear Dr. Jameson:

In response to the notice published in the Federal Register of February 3, 1998, 63 Fed. Reg. 5565, I am writing to provide the comments of the Nickel Development Institute ("NiDI"), the Nickel Producers Environmental Research Association ("NiPERA"), and Inco United States, Inc. ("Inco") on NTP's review of "Nickel Refining" and "Nickel and Nickel Compounds" for possible listing (or change of listing category) in the Ninth Report on Carcinogens. NiDI and NiPERA are organizations of the world's primary nickel producers. Their members are the principal suppliers of nickel to U.S. industry. Inco's Canadian parent company, Inco Ltd., is a member of NiDI and NiPERA. Inco and other NiDI and NiPERA member companies are committed to promoting the safe use of nickel metal and its alloys and compounds. They also seek to assure that sound science is applied in the classification and regulation of the various forms of nickel.

According to the Federal Register notice, Nickel and Nickel Compounds are being reviewed for a possible change from their current listing in the category of substances which may "reasonably be anticipated to be carcinogens"[1/] to the category of substances that are "known to be human carcinogens." The process of "Nickel Refining"-- which has not been identified as a "known" or "reasonably anticipated" carcinogen in the NTP's prior Reports on Carcinogens -- is being reviewed for possible listing under one or the other of these categories in the Ninth Biennial Report. For the reasons set forth below, we believe that neither of these actions is justified or appropriate.

1/ In the latest published Report (the Seventh Annual Report on Carcinogens), the "reasonably anticipated" listing is for "Nickel and Certain Nickel Compounds."

I. Nickel Refining Should Not Be Listed in the Ninth Biennial Report on Carcinogens.

NTP's Biennial Report on Carcinogens is published pursuant to Section 301(b)(4) of the Public Health Service Act. That provision directs the Secretary of the Department of Health and Human Services to "publish a biennial report which contains --

> "(A) a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed."[2/]

Given this statutory directive, there are two fundamental reasons why "Nickel Refining" should not be listed in the Ninth Biennial Report on Carcinogens.

First, in accordance with Section 301(b)(4) of the Public Health Service Act, unless something is a "substance," the Secretary has no authority to include it in a Biennial Report on Carcinogens. As the NTP acknowledges, manufacturing processes and occupations are not "substances" and, accordingly, "do not qualify for formal review for . . . listing [in the Report]." 61 Fed. Reg. at 55165/2. Since nickel refining is a manufacturing process, not a substance, it does not qualify to be reviewed for listing in the Ninth Biennial Report on Carcinogens.

Second, even if NTP were authorized to list manufacturing processes, nickel refining is not a process "to which a significant number of persons residing in the United States are exposed." In fact, no one in the United States is exposed to nickel refining, because nickel refining is no longer carried out in the United States. In recent years, there has been only one nickel refining operation in the United States, the Glenbrook Nickel Company's smelter near Riddle, Oregon, which previously had been operated by the Hanna Nickel Smelting Company. Earlier this year, Glenbrook, a subsidiary of Cominco Ltd., announced that it was closing its Riddle, Oregon nickel smelter and the associated port facility in Coos Bay, Oregon by March 30, 1998.[3/] With that closure, there will be no nickel refining in the United States; consequently, no one residing in the United States will be exposed to nickel refining. Thus, the second criterion for listing a substance in the Biennial Report on Carcinogens could not be met in the case of nickel refining.

Indeed, even if it were not closed, the Glenbrook Nickel smelter could not be considered to be the type of nickel refining process that is known or reasonably anticipated to be carcinogenic. The "nickel refining" processes where workers were found to have an increased incidence of respiratory cancer in epidemiological investigations involved the processing of

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[2/] 42 U.S.C. § 241(b)(4) (emphasis added).

[3/] A copy of the press release, along with a related newspaper article, is attached hereto.

sulfidic nickel ores in certain nickel refineries in Canada and Europe.[4] That type of nickel refining process has appropriately been viewed by the International Agency for Research on Cancer as being a Category 1 carcinogen -- at least in the conditions under which such refineries were operated earlier in this century.

In contrast to the Canadian and European nickel refineries which processed sulfidic nickel ores, however, Glenbrook, like its predecessor Hanna Nickel Smelting Company, processed lateritic nickel ores from Oregon and New Caledonia. In lateritic ores, nickel is present primarily in the form of nickel silicate and oxidic nickel, not in a sulfidic form.[5] Consequently, as the International Committee on Nickel Carcinogenesis in Man ("ICNCM") noted, no sulfidic nickel would be expected in the airborne particulate at the Riddle, Oregon refinery.[6] In this respect, Glenbrook differed significantly from the Canadian and European nickel refineries (processing sulfidic ores) where excess incidences of respiratory cancer were found.[7]

For this reason, even when it was operational, the Glenbrook nickel smelter in Riddle, Oregon could not properly be described as the kind of "nickel refining" process that the International Agency for Research on Cancer ("IARC") classified as being associated with an increased incidence of cancer. Indeed, the ICNCM's analysis of the epidemiological data for the Riddle, Oregon refinery found only a modest excess of lung cancer mortality, no malignancies of the nasal passages or sinuses, and no significant excess of any other type of cancer.[8] Moreover, there was no indication that the modest excess lung cancer mortality was related to time spent in jobs with the highest nickel exposure. To the contrary, the excess lung cancer incidence was attributable to a subgroup of short-term workers with less than one year of exposure. By

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[4] See "Report of the International Committee on Nickel Carcinogenesis in Man" (ICNCM Report), Scandinavian J. of Work, Environment & Health, Vol. 16, Number 1 (February 1990) *passim* (discussing the processes, exposures, and epidemiological findings at the INCO operations in Ontario, Canada and Clydach, Wales, and the Falconbridge operations in Ontario, Canada and Kristiansand, Norway).

[5] See Public Health Service, Agency for Toxic Substances and Disease Registry, Toxicological Profile for Nickel (Update), September 1997 (hereinafter "1997 Tox. Profile for Nickel") at 159-160.

[6] See ICNCM Report at 23.

[7] See ICNCM Report at 11-22.

[8] See ICNCM Report at 64.

contrast, workers with longer-term exposure (even those employed for 15 years or more) had no significant excess lung cancer mortality.[9/]

In sum, "Nickel Refining" clearly does not meet the criteria set forth in Section 301(b)(4) of the Public Health Service Act for listing in a Biennial Report on Carcinogens. Accordingly, it should not be reviewed further for possible inclusion in the Ninth Biennial Report.

II. Listing "Nickel and Nickel Compounds" as Known Human Carcinogens in the Ninth Biennial Report Would Be Scientifically Unjustified and Inappropriate.

The fundamental problem with NTP's proposal to list "Nickel and Nickel Compounds" as Known Human Carcinogens" in the Ninth Biennial Report on Carcinogens is that it fails to recognize the critical importance of speciation in evaluating the toxicity and potential carcinogenicity of the various forms of nickel. Each compound or species of a metal, like nickel, has its own physico-chemical properties that dictate how it behaves under a given set of conditions, including interactions with biological organisms.[10/] Thus, the fact that one form of nickel may be carcinogenic via a particular route of exposure (*e.g.*, inhalation) does not mean that a second nickel species will be carcinogenic as well or that the first nickel species will be carcinogenic via a different route of exposure (*e.g.*, ingestion). This observation holds true even if the free metal ion is assumed to be the active carcinogenic agent, because the different physico-chemical properties of various forms of the metal will largely determine the extent to which the free metal ion can be made bioavailable and delivered to a relevant biological site (such as the cell nucleus) within an organism. Accordingly, as the authors of a recent carcinogenicity assessment of nickel observed: "With regard to the carcinogenicity of nickel compounds, speciation is of paramount importance."[11/]

Against this background, the proposal to sweep metallic nickel and all nickel compounds into the single category of Known Human Carcinogens, as shown below, is inconsistent with both the epidemiological and toxicological literature, at odds with the best

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9/ See ICNCM Report at 64-65. A recent study of males having exposure to the mining or refining of lateritic nickel ores in New Caledonia also failed to find an increase in the incidence of respiratory cancer. Goldberg, M., *et al.* (1994). A 10-Year Incidence Survey of Respiratory Cancer and a Case-control Study Within a Cohort of Nickel Mining and Refining Workers in New Caledonia. Cancer Causes Control 5:15-25.

10/ See Conard, B., "Is Nickel Safe? A Toxicology Primer," in Pyrometallurgical Operations Environment Vessel Integrity in High-intensity Smelting and Converting Processes. C. Diaz, *et al.*, Editors. Proceedings of the Nickel-Cobalt 97 International Symposium-Vol. III, August 1997, Sudbury, Ontario.

11/ Oller, A., M. Costa & G. Oberdörster. Carcinogenicity Assessment of Selected Nickel Compounds (1997). Toxicology and Applied Pharmacology 143:152-166 at 163.

current understanding of the likely mechanism of nickel-related carcinogenicity, and without scientific support.

A. Epidemiology

Because of --

- mixed exposures to different nickel compounds, other inorganic compounds, and acids,
- sparse exposure data with little speciation or particle size information, and
- possible confounding effects of cigarette smoking,

most epidemiological studies of nickel-exposed occupational cohorts are difficult to interpret. In its comprehensive 1990 review of ten nickel-exposed cohorts, the International Committee on Nickel Carcinogenesis in Man concluded that "much of the respiratory cancer risk seen among the nickel refinery workers could be attributed to exposure to a mixture of oxidic and sulfidic nickel at very high concentrations."[12/] It also clearly found that there was "no evidence that metallic nickel was associated with increased lung and nasal cancer risks."[13/]

The ICNCM was unclear, however, regarding the role played by soluble nickel because the refinery exposures reviewed in the ICNCM Report always involved a mixture of soluble and insoluble compounds, and because the evidence regarding the potential carcinogenicity of soluble nickel compounds was inconsistent across the cohorts.[14/] In light of the uncertainty regarding the carcinogenic potential of various nickel species -- particularly soluble nickel -- the ICNCM looked forward to the results of the NTP inhalation bioassays for nickel subsulfide, high temperature green nickel oxide, and nickel sulfate hexahydrate that were then under way and to future work regarding the mechanisms of nickel carcinogenesis.[15/]

Following publication of the ICNCM Report, two relevant epidemiological studies have become available. One is a recent study in which no excess risk of nasal or lung cancer was found in nickel platers exposed solely to soluble nickel chloride and nickel sulfate mists[16/] The other is an update and supplemental analysis of high nickel alloys workers by Dr. Carol K. Redmond and co-investigators at the University of Pittsburgh Department of

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12/ ICNCM Report at 74.

13/ *Id.* at 74.

14/ See *id.* at 70-71, 74.

15/ *Id.* at 75.

16/ Pang, D. *et al.* (1996). Mortality Study of Nickel Platers with Special Reference to Cancers of the Stomach and Lung, 1945-1993. Occup. Environ. Med. 53:714-717.

Biostatistics.[17] The Redmond Study followed a cohort of 31,165 workers who were exposed, among other things, to metallic nickel and nickel oxide in 13 high nickel alloy production plants in the United States at some time between the late 1940s and mid 1960s. Their mortality experience was compared to the cause-specific mortality experience (adjusted for race, sex, age, and calendar time) of three comparison populations: the U.S. population as a whole; local populations in the geographical areas of the various plants; and an industrial population of steelworkers. As the authors explained in a summary of their Report:

> "Our findings suggest that the pattern of the risks derived for the various work areas and sex/race subgroups is similar across the three comparison populations, although elevated relative risks tend to be lower when the local population comparisons are used. Mortality from all causes or all malignant neoplasms is not increased. There is a 13% increased risk for lung cancer overall among nickel alloy workers when compared with the US population, but this excess is no larger than that which could be explained by some confounding factor such as cigarette smoking. In addition, comparisons made to the local populations show no excess."[18]

B. Inhalation Toxicology

The results of the NTP inhalation bioassays -- which were released formally in 1996 -- underscored the importance of speciation in assessing the carcinogenicity of nickel and created additional grounds for questioning whether soluble nickel, in and of itself, can be viewed as carcinogenic. In those bioassays,

- *Nickel subsulfide* showed clear evidence of carcinogenic activity in male and female rats, and no evidence of carcinogenicity in mice of either sex;
- *Green nickel oxide* showed some evidence of carcinogenic activity in male and female rats but no dose-response between the mid- and high-dose groups, no evidence of carcinogenic activity in male mice, and only equivocal evidence in female mice; and
- *Nickel sulfate hexahydrate* showed no evidence of carcinogenic activity in male or female rats and no evidence in male or female mice.[19]

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[17] Redmond, C., N. Sussman, V. Arena & J. Costantino. Supplemental Analysis of High Nickel Alloys Workers (Final Report December 15, 1995) ("Redmond Study").

[18] Redmond, C., *et al.* Update of the Mortality Experience of High Nickel Alloys Workers. September 12, 1996.

[19] See 61 Fed. Reg. 66054-66057 (December 16, 1996).

The NTP bioassay results are consistent with the findings of epidemiological studies in which -- (1) increased cancer risks have not been associated with exposure to soluble nickel alone; and (2) occupational cohorts exposed solely to soluble forms of nickel have not shown excess cancer risks. In combination, the epidemiological studies and NTP bioassays support the view that soluble nickel compounds by themselves are not likely to be respiratory carcinogens.

C. Mechanistic Considerations

Under NTP's updated carcinogen listing criteria, mechanistic information is considered in deciding whether to list a substance in (or remove it from) the Biennial Report on Carcinogens and in determining the category in which a listed substance should be placed.[20/] With that in mind, we call your attention to a recent article by Drs. Adriana Oller, Max Costa, and Günter Oberdörster which reviews the results of nickel-related epidemiological and toxicological studies and identifies the most likely mechanisms by which the carcinogenicity of various nickel compounds may be expressed. The authors observe that the various nickel species exhibit different biological behavior, and they suggest that the differential "ability of the compounds to be phagocytized and endocytized and their *in vivo* solubility may be the two most important characteristics to determine the bioavailability of Ni^{2+} at the target sites."[21/]

As pointed out by Drs. Oller, Costa, and Oberdörster, nickel subsulfide, *in vivo*, is likely to be readily endocytized and has a relatively high solubility in biological fluids; thus, it would be expected to be the most efficient nickel species in delivering the Ni^{2+} ion to a target site within the cell nucleus.[22/] At the same time, "[t]he release of Ni^{2+} could cause cell toxicity and directly induce inflammation and proliferation of initiated cells."[23/] Because it "may efficiently affect both components of the carcinogenic process, [nickel subsulfide] . . . appears to present the highest carcinogenic potential relative to other Ni compounds."[24/]

Green nickel oxide, by contrast, has a very low solubility in biological fluids and thus would be much less efficient in delivering the Ni^{2+} ion to a target site within the cell nucleus -- possibly requiring "overtly cytotoxic concentrations to see a heritable effect."[25/] Indeed, in the case of green nickel oxide, rat "tumors may be generated as a result of the

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20/ 61 Fed. Reg. 50499-50500 (September 26, 1996).

21/ See Oller, A., M. Costa & G. Oberdörster. Carcinogenicity Assessment of Selected Nickel Compounds (1997). Toxicology and Applied Pharmacology 143:152-166 at 163.

22/ See *id.* at 160.

23/ *Id.*

24/ *Id.*

25/ See *id.* at 161.

inflammatory/proliferative response that results from chronic activation of macrophages rather than due to a direct heritable effect of Ni^{2+}."[26] That is, tumorigenesis associated with green nickel oxide may reflect the operation of a "particle effect" in which lung tumors are produced as a secondary response to impaired clearance.[27]

Soluble nickel does not readily cross mammalian cell membranes *in vivo*, and, when it does, the Ni^{2+} ions bind to cytoplasmic ligands and thus "will not accumulate in the cell nucleus at the concentrations needed to have a genetic effect."[28] Furthermore, because soluble nickel is rapidly cleared from the respiratory tract, "no efficient delivery of Ni^{2+} to the target site (within the cell nucleus) is expected."[29] Accordingly, soluble nickel is most likely to act as a promoter of cell proliferation (following the induction of cell toxicity and inflammation), rather than as an agent that induces a heritable genetic change on its own.[30]

Taking into account the results of epidemiological and animal studies as well as these mechanistic considerations, Drs. Oller, Costa, and Oberdörster conclude that:

> "● nickel subsulfide is likely to be carcinogenic to humans;
>
> ● nickel sulfate hexahydrate, by itself, is not likely to be carcinogenic to humans (although, because soluble compounds can cause toxicity and cell proliferation, an enhancing effect on carcinogenicity of insoluble nickel compounds is possible and more animal studies are needed to test the presence of this effect); and
>
> ● green nickel oxide (NiO calcined above 1000° C) may only be carcinogenic to animals and humans at high doses that result in chronic inflammation/cell proliferation, even though *in vitro*, equitoxic concentrations of green NiO (10-fold higher) can induce some of the same effects seen with Ni_3S_2."[31]

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[26] *Id.*

[27] See *id.* at 159-161. This "particle effect" may occur at lower concentrations for particles of intermediate toxicity, such as green nickel oxide, than for particles of very low toxicity, such as carbon black, titanium dioxide, or talc. See Oberdörster, G. (1995). Lung Particle Overload: Implications for Occupational Exposures to Particles. Regul. Toxicol. Pharmacol. 21:123-135.

[28] Oller, *et. al.*, supra at 161.

[29] *Id.*

[30] *Id.* at 161-162.

[31] *Id.* at 163.

D. Assessments by EPA, ACGIH, and ATSDR

In light of the foregoing, it is not surprising that various agencies and public health bodies have distinguished among different nickel species for purposes of cancer classification. For example, U.S. EPA has classified nickel subsulfide and nickel refinery dust from pyrometallurgical sulfide nickel matte refining as Group A Human Carcinogens and nickel carbonyl as a Group B2 Probable Human Carcinogen.[32/] EPA has considered the evidence for other nickel species to be inadequate to make a determination regarding cancer classification.[33/]

The American Conference of Governmental Industrial Hygienists ("ACGIH") also differentiates among the various nickel species for purposes of cancer classification. In November 1997, ACGIH adopted three different carcinogen designations for the various nickel species as part of its Threshold Limit Value ("TLV") program.

- Nickel subsulfide was placed in Category A1 - Confirmed Human Carcinogen;
- Insoluble nickel compounds were placed in Category A1 - Confirmed Human Carcinogen;
- Soluble nickel compounds were placed in Category A4 - Not Classifiable as a Human Carcinogen; and
- Elemental/metallic nickel was placed in Category A5 - Not Suspected as a Human Carcinogen.[34/]

In its most recent Update of the Toxicological Profile for Nickel, the Agency for Toxic Substances and Disease Registry ("ATSDR") also distinguished among different nickel species in its assessment of potential carcinogenicity. This reflected ATSDR's conclusion that, in assessing the potential health effects of nickel, "it is important to consider what form of nickel a person is exposed to and its bioavailability."[35/] In its species-specific evaluations, ATSDR deemed the evidence "sufficient to consider less-soluble nickel compounds [particularly nickel subsulfide] carcinogens following inhalation exposure," but noted that "soluble nickel compounds may not be directly carcinogenic."[36/] Instead, ATSDR observed, soluble nickel may

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32/ See EPA's Integrated Risk Information System ("IRIS") database entries for "Nickel subsulfide" (March 1, 1997) and "Nickel refinery dust" (March 1, 1997).

33/ See 51 Fed. Reg. 34135 (September 25, 1986).

34/ See ACGIH, 1997 TLVs® and BEIs® at 42-43 (Notice of Intended Changes). These proposed TLV recommendations and carcinogen classifications were ratified as "adopted" values by the ACGIH Board of Directors on November 1, 1997.

35/ 1997 Tox. Profile for Nickel at 199.

36/ See 1997 Tox. Profile for Nickel at 130-131.

"serve to promote carcinogenesis" as a result of causing an inflammatory response in lung tissue.[37] The Agency also emphasized that "[n]o evidence was found that metallic nickel causes respiratory cancer."[38]

E. Oral Route of Exposure

The foregoing discussion relates to the potential carcinogenicity of various nickel species via inhalation. As noted above, the results for the inhalation route of exposure are mixed -- varying from relatively strong evidence of carcinogenicity for nickel subsulfide to negative findings for metallic nickel. By contrast, there are no findings of increased cancer risk in humans following oral exposure to nickel, and all five animal studies involving chronic oral exposure to nickel have been negative.[39] As U.S. EPA observes, in the case of nickel, "data by the oral route show no evidence of carcinogenicity."[40] Thus, whatever may be the case with respect to inhalation of certain nickel species, there is no basis for suggesting that any form of nickel is carcinogenic via the oral route of exposure.[41]

F. NiDI-NiPERA-Inco Recommendations

As the foregoing discussion indicates, there is no scientific justification for listing "Nickel and Nickel Compounds" in the aggregate as Known Human Carcinogens in NTP's Ninth Biennial Report. Instead, species-specific determinations must be made.

Under NTP's revised criteria, a substance may be listed as "Known To Be a Human Carcinogen" where "[t]here is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer."[42]

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[37] See *id.* at 131.

[38] *Id.* at 54.

[39] Schroeder, H., *et al.* (1964). Chromium, Lead, Cadmium, Nickel and Titanium in Mice: Effect on Mortality, Tumors and Tissue Levels. J. Nutr. 83:239-250; Schroeder, H., *et al.* (1974). Life-term Effects of Nickel in Rats: Survival, Tumors, Interactions with Trace Elements and Tissue Levels. J. Nutr. 104:239-243; Schroeder, H. & M. Mitchener (1975). Life-term Effects of Mercury, Methyl Mercury, and Nine Other Trace Metals on Mice. J. Nutr. 105(4):452-458; Ambrose, A., *et al.* (1976). Long Term Toxicologic Assessment of Nickel in Rats and Dogs. J. Food Sci. Technol. 13:181-187.

[40] 57 Fed. Reg. 31776, 31786 (July 17, 1992).

[41] There also are no studies suggesting that nickel is carcinogenic to humans or animals via dermal exposure. See 1997 Tox. Profile for Nickel at 90.

[42] 61 Fed. Reg. 50499 (September 26, 1996).

Under the revised criteria, a substance may be listed as "Reasonably Anticipated To Be a Human Carcinogen" where:

> "There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded, or
>
> "There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant and/or combined benign and malignant tumors: (a) in multiple species or at multiple tissue sites, or (b) by multiple routes of exposure, or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset."[43/]

Applying these criteria to the overall weight of the evidence for the various nickel species leads us to suggest the following as appropriate carcinogen classifications:

Nickel subsulfide -- Known To Be a Human Carcinogen.

Green nickel oxide and other water-insoluble nickel compounds -- Reasonably Anticipated To Be a Human Carcinogen. Because of the mixed exposures in the refinery studies, a causal interpretation is credible, but the results are confounded by co-exposure to sulfidic nickel. In addition, members of a cohort of more than 31,000 high nickel alloy workers exposed to nickel oxide and metallic nickel (but not to sulfidic nickel) were not found to have an increased risk of lung cancer in the Redmond Study.

Nickel sulfate hexahydrate and other soluble nickel compounds -- Should not be listed in the Ninth Biennial Report at all because:

(1) In epidemiological studies, increased cancer risks have not been associated with exposure to soluble nickel alone, and occupational cohorts exposed solely to soluble forms of nickel have not shown excess cancer risks;

(2) The results in animal studies by both the inhalation and oral route of exposure have consistently been negative; and

(3) Mechanistic considerations point to the conclusion that soluble nickel by itself is not likely to be carcinogenic to humans, but instead may enhance the carcinogenic effect of other agents by causing cytotoxicity and resulting cell proliferation.

43/ *Id.*

In these circumstances, as ACGIH recently recognized, soluble nickel is not classifiable as a human carcinogen and should not be classified as such in the Ninth Biennial Report.

Metallic/elemental nickel -- Should not be listed in the Ninth Biennial Report at all because there is no evidence of a causal relationship in human studies, and the only animal studies showing a clear tumorigenic response involved the route of injection (primarily injection-site tumors). As EPA observes, "inhalation studies have not shown that nickel in the metallic form will produce respiratory tract tumors," and, even when the intramuscular injection studies are considered, the "tests are presently inadequate to support any definitive conclusions regarding . . . [the] carcinogenicity [of metallic nickel]."[44/] Since there is no evidence for the carcinogenicity of metallic nickel via inhalation or ingestion in epidemiological or animal studies,[45/] and since no one is exposed to metallic nickel via the route of injection, there is no basis for "reasonably anticipating" that metallic nickel is carcinogenic to humans via a route that is relevant to the potential exposures of persons residing in the United States.

Conclusion

For the reasons set forth above, "Nickel Refining"should not be included in the Ninth Biennial Report on Carcinogens, and "Nickel and Nickel Compounds" should not be listed as Known Human Carcinogens. Instead, NTP should make species-specific carcinogen determinations for the various forms of nickel, taking into account the recommendations presented in Part II.F. above.

If you have any questions about the points discussed in this comment letter, please let me know.

Very truly yours,

Neil J. King

Neil J. King

Counsel for the Nickel Development Institute, the Nickel Producers Environmental Research Association, and Inco United States, Inc.

44/ U.S. EPA, Health Assessment Document for Nickel and Nickel Compounds (Final Report September 1986) at 8-109, 8-113.

45/ See 1997 Tox. Profile for Nickel at 54; ICNCM Report at 74.